# Prediction of the insulin sensitivity index using Bayesian networks

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# Prediction of the Insulin Sensitivity Index using Bayesian Networks

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# Prediction of the insulin sensitivity index

- The insulin sensitivity index ($S_I$) can be used in assessing the risk of developing type 2 diabetes.
- Is determined by observations from an intravenous glucose tolerance test using Bergmans minimal model and estimated by a non-linear least squares estimation technique.
- Goal is to determine this index from an oral glucose tolerance test, to be used in large scale epidemiological studies.
- Idea: Learn Bayesian network with observations from an oral test and the index determined from an intravenous test.
- As learning tool, use the software package deal, written for R.
- Export the final network to Hugin to calculate the predictive distribution of $S_I$.

# Bayesian Network

We define it as:

- A Directed Acyclic Graph (DAG) $D = (V, E)$.
- Set of variables associated with D is $X = (X_v)_{v \in V}$.
- To each vertex $v$ with parents $pa(v)$, there is attached a local probability distribution, $p(x_v | x_{pa(v)})$.
- Possible lack of edges in D encodes conditional independencies,

$$p(x) = \prod_{v \in V} p(x_v | x_{pa(v)}).$$

# Parameter learning

- Continuous variables are Gaussian linear regressions on the continuous parents, and have therefore jointly a Gaussian distribution.
- Parameter learning

$$p(\theta|data) \propto p(data|\theta)p(\theta).$$

- Assume parameter independence and complete data. Posterior parameter independence follows.
- Conjugate prior distribution Gaussian - inverse Wishart.

# Structure Learning

- Structure learning

$$\mathrm{p}(\mathrm{DAG}|\mathrm{data}) \propto \mathrm{p}(\mathrm{data}|\mathrm{DAG})\mathrm{p}(\mathrm{DAG}).$$

- If all DAGs equally likely

$$\mathrm{p}(\mathrm{DAG}|\mathrm{data}) \propto \mathrm{p}(\mathrm{data}|\mathrm{DAG}).$$

- Network score decomposable.
- The likelihood is given as

$$\mathrm{p}(\mathrm{data}|\mathrm{DAG}) = \int_{\theta} \mathrm{p}(\mathrm{data}|\theta, \mathrm{DAG})\mathrm{p}(\theta|\mathrm{DAG})\mathrm{d}\theta.$$

- Automated procedure for finding $\mathrm{p}(\theta|\mathrm{DAG})$ for all possible DAGs.

# Master Prior Procedure

(Geiger and Heckerman (1994))

- Random variables have joint Gaussian distribution

$$(\mathbf{y}|\mathbf{m}, \Sigma) \sim \mathcal{N}(\mathbf{m}, \Sigma).$$

- Let joint parameter prior be Gaussian-inverse Wishart,

$$(\mathbf{m}|\Sigma) \sim \mathcal{N}(\mu, \frac{1}{\nu}\Sigma) \text{ and } (\Sigma) \sim \mathcal{IW}(\rho, \Phi).$$

  By marginalizing and conditioning, parameters for each parent-child relationship can be found.

- Parameters are independent, so joint prior is the product of the local priors.

- To specify master prior $\mathcal{N}(\mu, \frac{1}{\nu}\Sigma)$ and $\mathrm{IW}(\rho, \Phi)$, specify prior network $(\mathrm{D}, \mathcal{P})$ and sample size of imaginary database.

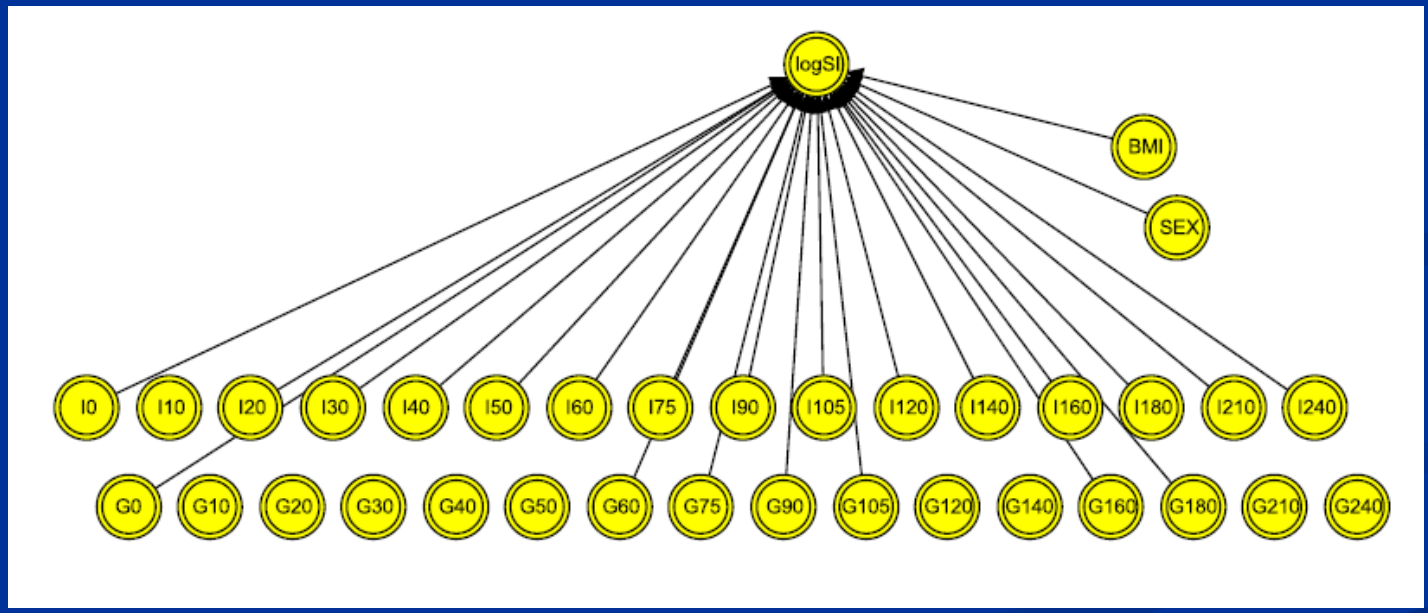
# Software: deal

- `deal`: A package for R.
- Downloads from CRAN `http://cran.R-project.org/`.
- Graphical interface.
- Local master prior procedure for determining parameter priors for all networks.
- Parameter learning.
- Calculation of network score.
- Structure learning using greedy search (with random restarts).
- Simulation of datasets.

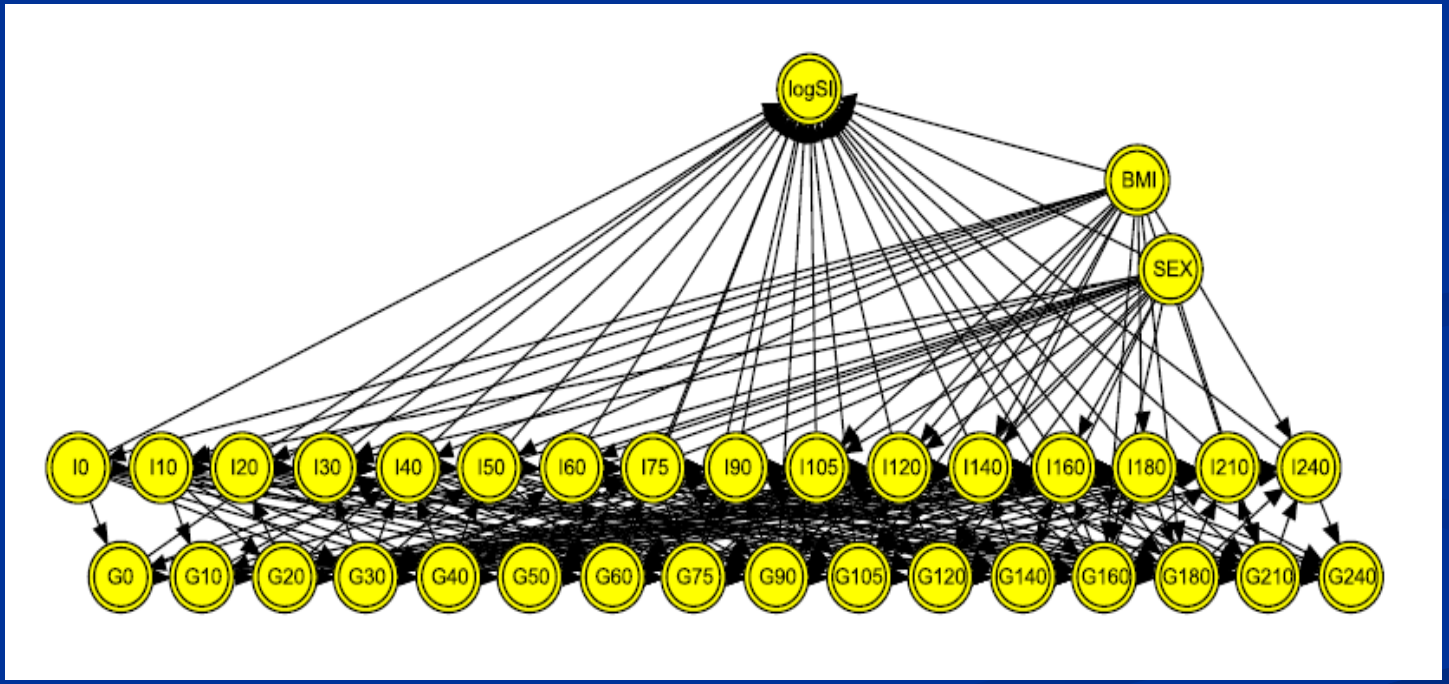
# Data

- 187 non-diabetic glucose tolerant subjects underwent both an OGTT and an IVGTT.
- 140 subjects used as training data and 47 subjects used as validation data.
- $\log S_I$ for each subject calculated from the IVGTT using Bergmans minimal model.
- Glucose and insulin concentrations determined in the OGTT at 0, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 140, 160, 180, 210 and 240 minutes.
- Other variables BMI and sex. Sex modelled as a continuous variable.

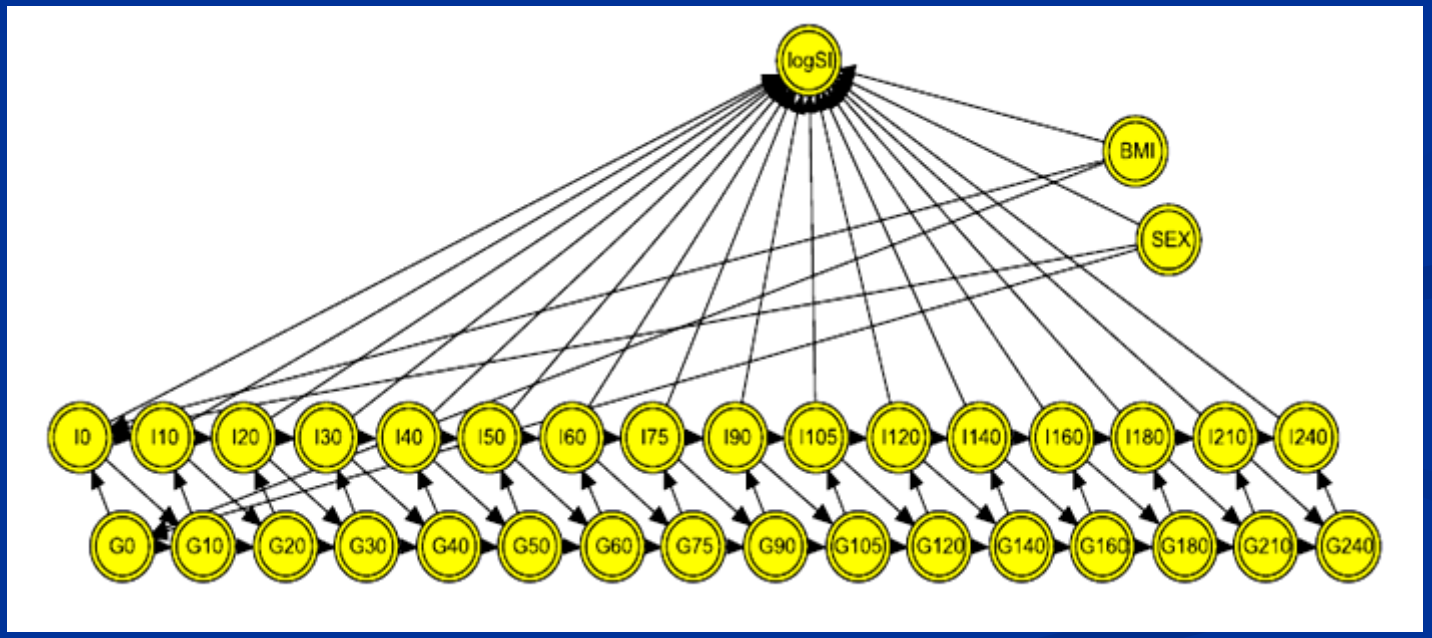
# Bayesian Regression Network



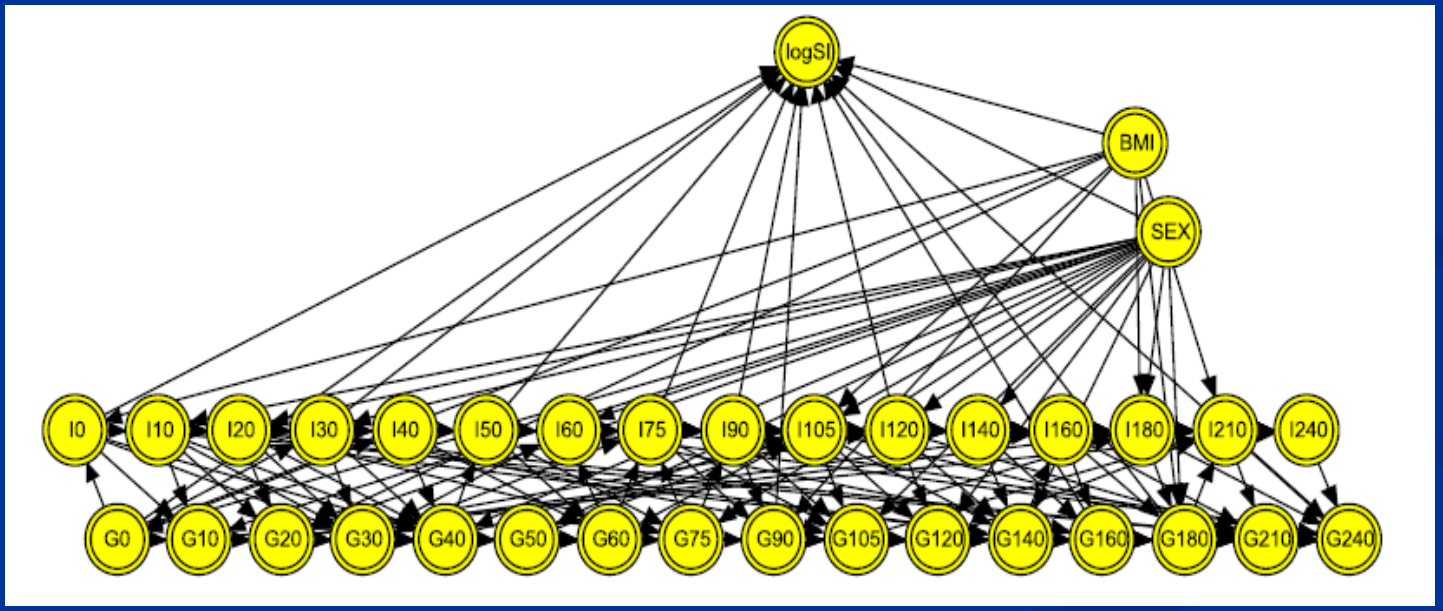
# Bayesian Network with empty prior



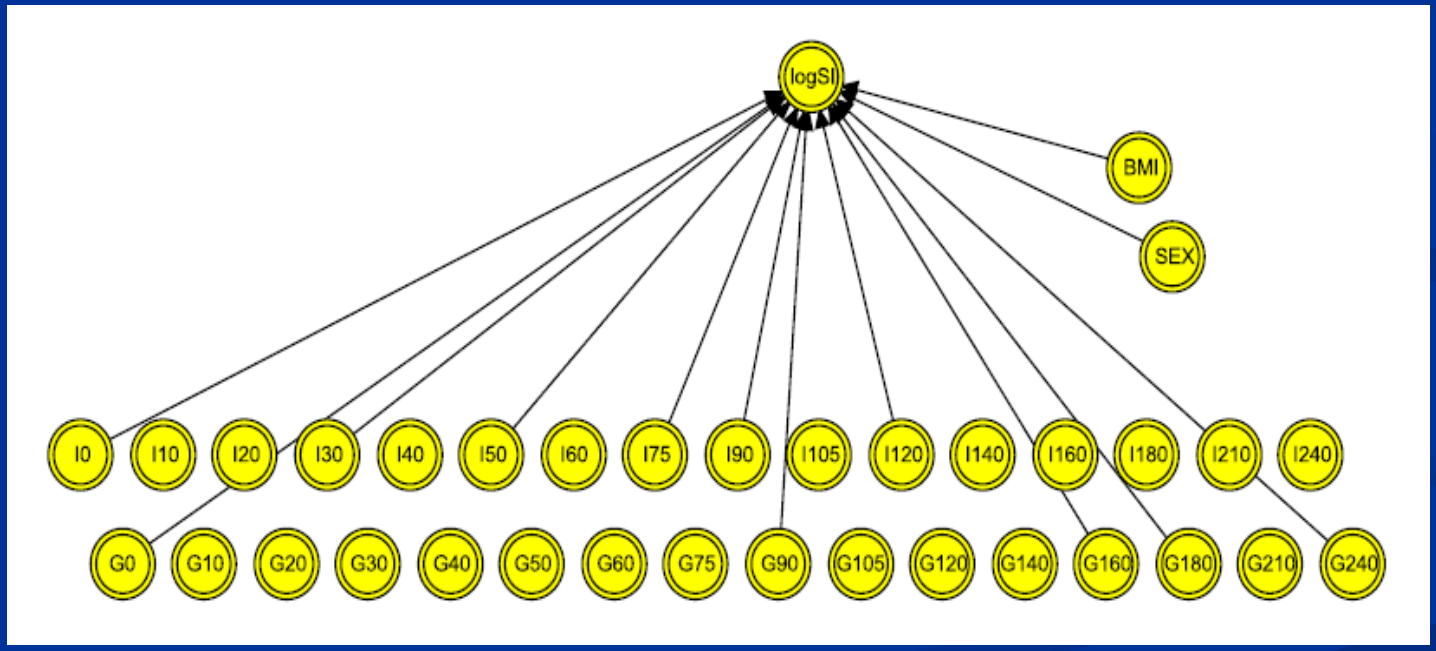
# The physiological Network



# Bayesian Network with physiological prior



# Markov Blanket with physiological prior



# Results using multiple linear regression

Previous result (Drivsholm et al. (2003)) using multiple linear regression:

$$\log S_I \sim \quad BMI + SEX + G0 + I0 + G30 + I30 + G60 + I60 + G105 + I105 + G180 + I180 + G240 + I240$$

Result using leaps and bound algorithm for best subset selection:

$$\log S_I \sim \quad BMI + SEX + I50 + I90 + G160$$

# Evaluation

- Network scores (log scores).
- For each subject the conditional distribution of $\log S_I$ is calculated given the observations from the OGTT using Hugin (the predictive distribution of $\log S_I$).
- 95%'s credibility intervals $\mu \pm 1.96 \cdot \sigma$ for det predictive distribution of $\log S_I$ is calculated. Examine whether 95 $\%$ of the corresponding IVGTT $\log S_I$ values lie within this interval. If so, the predictive distribution of $\log S_I$ is *well calibrated*.
- Residual standard deviation (SD) and correlation coefficient, ($R^2$) obtained from a linear regression of the IVGTT obtained $\log S_I$ on the predicted $\log S_I$. To see if there is systematic bias in these regressions, the intercept and slope of these regressions lines are reported.

# Network scores

| Model | Empty prior | Physiological prior |
|---|---|---|
| BR | −17878.30 | −17848.33 |
| BN | −16528.39 | −14851.44 |
| MLR | −17886.17 | −17849.06 |
| L&B | −17894.95 | −17846.12 |

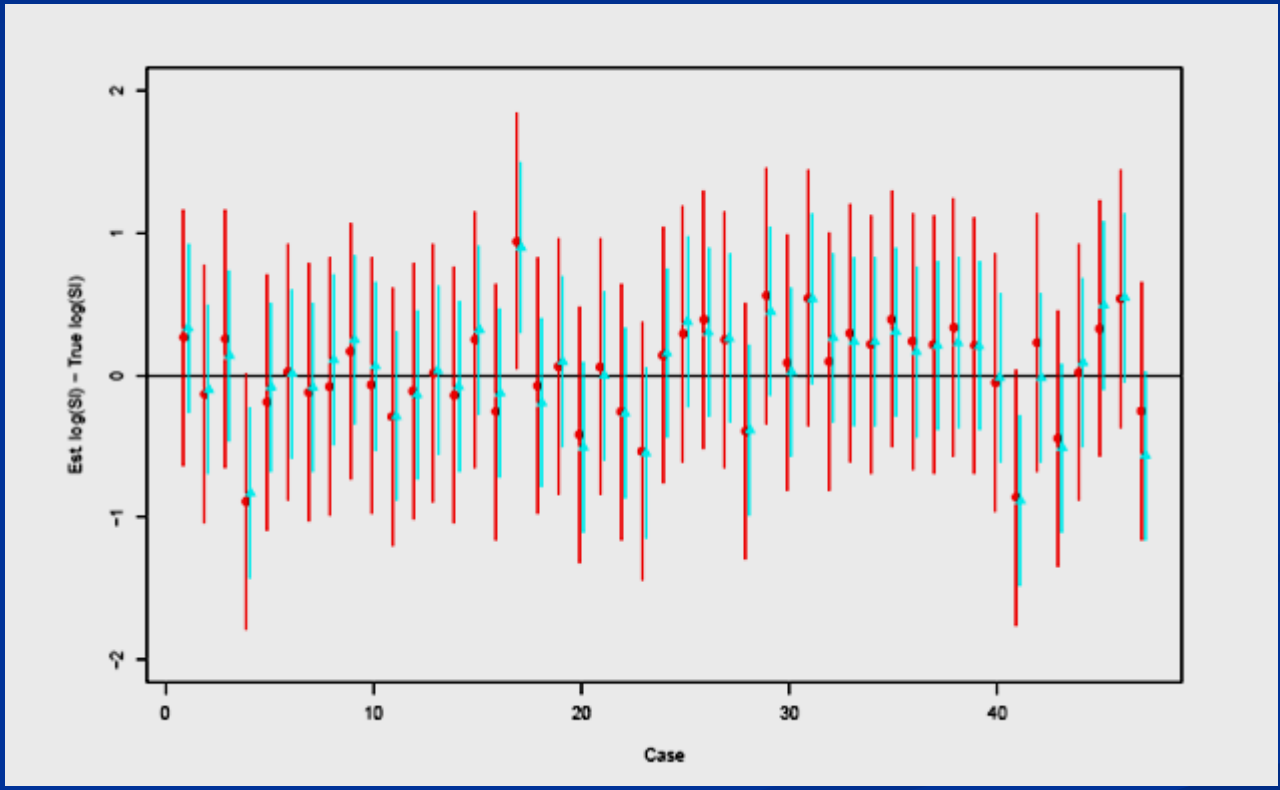
# Intercept and slope for regression of IVGTT obtained index on predicted index

| Model | Tr. data (intercept, slope) | Val. data (intercept, slope) |
|---|---|---|
| BR empty prior | $(-0.19, 1.09)$ | $(-0.05, 1.01)$ |
| BN empty prior | $(-0.03, 1.01)$ | $(0.25, 0.87)$ |
| BN phsy. prior | $(-0.06, 1.03)$ | $(0.14, 0.92)$ |
| MLR | $(0, 1)$ | $(0.06, 0.96)$ |
| L&B | $(0, 1)$ | $(0.11, 0.93)$ |

# $R^2$ and SD from the regression and also number of values outside credibility intervals.

| Model | Tr. data $R^2$ (SD) | Val. data $R^2$ (SD) | Tr. outside | Val. outside |
|---|---|---|---|---|
| BR with empty prior | 0.76(0.31) | 0.73(0.35) | 1(1%) | 1(2%) |
| BN with empty prior | 0.76(0.31) | 0.73(0.35) | 1(1%) | 1(2%) |
| BN with phys. prior | 0.77(0.30) | 0.73(0.36) | 7(5%) | 3(6%) |
| MLR | 0.76(0.31) | 0.66(0.40) | 3(2%) | 3(6%) |
| L&B | 0.75(0.31) | 0.73(0.36) | 6(4%) | 4(9%) |

# Predicted index and credibility intervals – empty prior red and disks, physiological prior green and triangles



# Summary

- All approaches give adequate predictions of $S_I$.
- Bayesian network with physiological prior estimates most precise predictive distribution of $S_I$.
- Can use any prior knowledge available from e.g. previous studies or the physiological understanding of the problem.
- Predictive distribution of $S_I$ can be calculated in situations with missing observations - here the correlations between the insulin and glucose observations are important.

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